Targeted therapy, molecular imaging and biomarkers in cancer treatment

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Chapter 7

Summary and future perspectives

SUMMARY

In recent years, great progress has been made in the development of targeted therapy against cancer. However, it is also more recognized that these treatments are often only successful in a subgroup of patients. One of the current challenges in oncology lies in identifying these patients and thereby avoiding treating patients with non-effective treatments and thus avoid side-effects of these drugs and reduce costs. Another challenge in oncology is to minimize the side effects of currently used therapies. Patients are at risk for developing (long term) and even deadly side effects of anticancer treatments and might need adjustments to their treatment schedule and specific follow up long after the end of treatment to timely recognize and address these.

One of the targeted therapies that made its way into clinical research in recent years is the induction of apoptosis by agonistic antibodies or rhTRAIL via the extrinsic pathway. In preclinical studies, these drugs have been shown to induce apoptosis as monotherapy and enhance the effectiveness of chemotherapy and radiotherapy. In **chapter 2**, we reviewed the phase 1 and phase 2 (combination) studies that have been performed with these drugs. Although rhTRAIL and the diverse agonistic antibodies against TRAIL-R1 and TRAIL-R2 all seem safe with only one maximum tolerated dose found for lexatumumab (elevations of serum amylase, bilirubin and transaminases), the effectiveness of these drugs both as monotherapy and in combination with chemotherapy is disappointing. However, we also describe novel approaches with TRAIL linked to a tumor specific antibody that might lead to better results in the clinic. Also, the combination of mapatumumab with chemotherapy and radiotherapy was investigated in a phase 1/2 study (NCT01088347). Results of this study are awaited.

When the targeted drug imatinib entered the clinic in early clinical studies in patients with GIST it was noticed that within one to several days a remarkable change in FDG uptake in the tumors occurred. It was suggested that this change in uptake could serve as a predictive marker for the efficacy of this therapy. Several small studies with FDG-PET in this setting have been conducted since, leading to variable results. However, it has become clear that the majority of patients (85%) have clinical benefit from this treatment. A predictive test that identifies patients that have clinical benefit would therefore not be that informative, but a test that identifies patients that will not respond (primary resistance) is. In **chapter 3** we retrospectively assessed the usefulness of FDG-PET scans made before start of imatinib and 1 week after start of imatinib for identification of non responders. Two out of 29 patients showed progressive disease on CT scan after 8 weeks as defined by the RECIST criteria. These patients also showed a response (defined as at least 25% decrease in standard uptake value (SUV)) on the FDG-PET scan. On the other hand the three patients who did not show a response on the FDG-PET scan all did have clinical benefit of imatinib. We therefore concluded that performing a FDG-PET scan is not useful in identifying patients with primary resistance against imatinib and that the early responses seen on FDG-PET scan might be caused by a change in glucose metabolism that is independent of the tumor response.

In glioblastomas the Macdonalds criteria are used for response assessment and the tumor is measured as the contrast enhancing area found on gadolinium enhanced MRI. Response assessment during and after treatment is hampered by the phenomenon of pseudoprogression: the MRI performed directly after completion of chemoradiotherapy shows increased contrast enhancement compared to the baseline MRI, but this enhancement remains stable or subsides on follow up scans without change of therapy. In **chapter 4** we reported on a study that prospectively assessed FLT-PET scans made before start of treatment (after initial surgery) and 4 weeks after completion of chemoradiotherapy. ^{18}F-FLT is a PET tracer that is taken up by proliferating cells and therefore it might potentially be of interest to use FLT-PET scans to discriminate between true tumor growth and pseudoprogression. In 24 evaluable patients, seven patients showed true progression and seven showed pseudoprogression on MRI. We observed no difference in (change in) FLT uptake between patients classified as true progression and patients classified as pseudoprogression. Therefore FLT-PET scan in this setting cannot be used to discriminate between true disease progression and pseudoprogression in glioblastoma patients treated with chemoradiotherapy.

In high grade gliomas successful targeted drugs are also eagerly awaited, as there is currently no standard therapy for recurrent disease and the median overall survival for the most common subtype (glioblastoma) is only 14 months. Numerous targeted agents have been investigated in recent years, but so far no therapy has improved the overall survival. A key question in systemic treatment of high grade gliomas is if the agents can reach the tumor because of the blood brain barrier. In **chapter 5** we reported on a study in which a monoclonal antibody against TGF-β (fresolimumab) was labeled with Zirkonium-89. After the ^{89}Zr-fresolimumab PET scan, patients were treated with intravenously administered fresolimumab. The goal of this study was to show that the antibody could reach the tumor and to quantify the uptake and correlate this uptake with the outcome of treatment with fresolimumab. In all 12 patients we saw uptake of ^{89}Zr-fresolimumab in tumor lesions, although not in all individual lesions. Of the lesions that were > 1 cm and not visible on the PET scan, 2 out of 3 were previously irradiated and might therefore not represent active tumor tissue with TGF-β signaling. We also found that over time the tumor to blood ratio increased in four patients who underwent a PET scan on both day 2 and day 4 after the tracer injection. These findings suggest that the uptake of ^{89}Zr-fresolimumab in the tumor is specific rather than just a perfusion related phenomenon. Treatment with fresolimumab was well tolerated by all patients, but it did not seem to be beneficial in terms of inducing tumor response as second line treatment. However, we did show that a labeled antibody is able to reach high grade gliomas.

TGF-β is important in many processes in both health and disease. From preclinical research, we know that TGF-β plays an important role in the development of bleomycin induced pulmonary toxicity. This toxicity is a problem in testicular cancer patients that are treated with bleomycin containing chemotherapy regimens. This treatment has a very high cure rate, but in up to 10% of the patients bleomycin induced pulmonary toxicity occurs, which is fatal in 10% of patients experiencing this toxicity. In **chapter 6** we assessed the prevalence of lesions

suspect for bleomycin-induced pulmonary changes on restaging CT scans after treatment, and whether the fibrosis markers TGF-β1 and Growth Differentiation Factor -15 (GDF-15), and hs-CRP were predictive of this. We found signs of bleomycin-induced pulmonary changes on the restaging CT scan in 68% of the patients. Plasma levels of TGF-β1, GDF15 and Hs-CRP were not predictive for the occurrence and severity of CT alterations suspect for bleomycin toxicity or clinical pulmonary toxicity. We concluded that bleomycin-induced pulmonary changes are very common on restaging CT scans after BEP chemotherapy for metastatic testicular cancer, but plasma levels of TGF-β1, GDF15 and Hs-CRP cannot be used as biomarkers for this.

FUTURE PERSPECTIVES

The recent rapid unraveling of tumor characteristics and the use of these insights for the application of targeted therapy has led to hope that cancer will become a chronic disease in the coming years [1]. In spite of this optimism, it has also become clear that new discoveries and developments raise new questions and challenges.

In metastatic and irresectable GIST tumors, the introduction of the targeted drug imatinib spectacularly improved response rates compared to chemotherapy. Unfortunately, many targeted drugs that seemed promising in preclinical research did not live up to the expectations in phase 1 and 2 studies. Agonistic antibodies against TRAIL receptors and rhTRAIL are well tolerated and can be combined with chemotherapy. However, none of the randomized phase 2 studies so far has shown an improvement of progression free survival or overall survival. This underlines the enormous challenges in finding drugable targets, identifying patients that will benefit from treatment with targeted drugs, the need for rational combination therapies and perseverance when clinical results do not directly live up to the expectations found in preclinical research.

In glioblastomas, driver mutations and pathways are still not elucidated and there is no targeted agent available that does improve overall survival [2]. Although TGF-β is an important tumor promoter in these tumors, treatment with fresolimumab did not result in clinical benefit in our small study with pretreated patients. Since many pathways are deregulated in high grade gliomas, better results might be expected from combination treatment targeting multiple relevant pathways. Since we did show in our study that fresolimumab is able to reach brain tumors, other antibody-related drugs such as antibody-drug conjugates are also of potential interest for this indication (NCT01475006).

A key requirement in successful anticancer drug development is to establish the molecular and genetic characteristics of tumors. Studies in which biopsies are taken before and after (investigational) treatment with targeted agents are currently performed and will learn us more about tumor characteristics, patient selection and development of resistance mechanisms against targeted agents. In the future, this will lead to more personalized medicine, in which a patient receives a treatment based on the specific characteristics of the tumor.

However, it is also known that primary tumor lesions and metastatic lesions can have different characteristics and tumor characteristics can change over time [3]. Taking multiple

biopsies at different time points to characterize the heterogeneity will often not be feasible due to patient inconvenience and tumor lesions that cannot be approached safely. Molecular imaging is a more patient friendly approach to assess the characteristics of all different tumor lesions. Diverse studies show promising results with this approach [4,5]. However, we showed that the initial optimism about the use of FDG-PET to predict responses of imatinib in GIST has been premature. Furthermore, response criteria for PET imaging still need to be established and might be different for different PET tracers. More and larger studies establishing this and studies directly comparing PET results with pathology results are therefore urgently needed and are currently performed (NCT01957332).

Since the introduction of targeted agents in the clinic it has also become clear that the current response assessment with CT scans may be suboptimal because targeted agents do not always induce a volume response. Initiatives to define new criteria in which also PET responses might be included are under investigation [6]. In brain tumors the Macdonalds criteria have already been replaced by the RANO criteria, in order decrease the number of pseudoprogression and pseudoresponses found [7]. However, for this indication also a combination of conventional imaging and molecular imaging will be needed to accurately assess responses of current and future therapies. We showed that serial FLT-PET scan was not helpful in discriminating pseudoprogression from true progression in primary glioblastoma patients treated with chemoradiotherapy. However, approaches using other parameters such as kinetic analysis may overcome the difficulty of discriminating between tracer uptake and leakage due to a disrupted blood brain barrier. Also other imaging modalities such as perfusion MRI and ^{11}C-methionine-PET show promising results and are currently under more detailed investigation [8,9].

An interesting development in imaging that circumvents the irradiation burden of PET scans is optical imaging. Its use is currently limited by the tissue penetration of the optical tracers which makes whole body scanning impossible, but it is especially investigated for surgical applications. Since optimal surgical resection is one of the predictive markers for overall survival in glioblastoma, tumor resection using optical imaging with a specific tracer might be a promising tool to discriminate infiltrating tumor from normal brain tissue [10,11].

With the increasing number of cancer patients and improvements in treatment, the number of cancer survivors is also increasing [12]. Long term effects of anticancer treatments are therefore gaining more attention. We know that particular attention needs to be paid to cardiovascular diseases and secondary malignancies in long term cancer survivors [13]. Biomarkers may help to identify patients at risk for long term and harmful side effects. A challenge for the future will be to prevent predicted (long term) toxicity without jeopardizing the efficacy of anticancer treatments resulting in a balanced trade-off.

In conclusion, notwithstanding the enormous challenges ahead, cancer medicine will become more and more personalized: new imaging techniques will be able to reveal tumor characteristics, specific drugs will be able target these, specific patients characteristics will be taken into account and the follow up of patients will be aimed at the specific long term effects based on the therapy and risk factors of the individual patient.

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7